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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,992	10/04/2006	Russell John Stewart	00846-U3051.PCT.US	5509
20551 7590 07/21/2011 THORPE NORTH & WESTERN, LLP. P.O. Box 1219 SANDY, UT 84091-1219			EXAMINER KOSAR, AARON J	
			ART UNIT 1657	PAPER NUMBER
			NOTIFICATION DATE 07/21/2011	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/567,992	STEWART ET AL.	
	Examiner	Art Unit	
	AARON KOSAR	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 April 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-79 is/are pending in the application.
- 4a) Of the above claim(s) 30 and 45-79 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24, 26-29 and 33-44 is/are rejected.
- 7) ☒ Claim(s) 25 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 April 2011 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

Applicant's amendment and argument filed April 20, 2011, in response to the non-final rejection, are acknowledged and have been fully considered. Any rejection and/or objection of record not specifically addressed is herein withdrawn.

Claims 1-79 are pending of which claims 30 and 45-79 remain withdrawn as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-29 and 31-44 are pending and have been examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-24, 26, 27 and 31-44 stand as rejected under 35 U.S.C. 103(a) as being unpatentable over Gill *et al* ("Nickel-dependent oxidative cross-linking of a protein" Chem. Res. Toxicol. March 1997, 10(3), 302-9.).

The claims are drawn to a method comprising attaching a metal ligand to a first moiety, a metal ligand to a second moiety, and adding a metal ion to form a coordination complex between the first and second moiety.

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Gill teaches that a method comprising forming by the action of horseradish peroxidase (metalloenzyme) and H_2O_2 (oxidant), and which is known to couple proteins (first and second moieties) via formation of dityrosine (phenolic metal ligands added to the first and second moieties; covalent crosslink), and that free Ni^{2+} (metal ion) intrinsically and spontaneously binds to peptide backbones, creating metal-peptide sites (to form a coordination complex between the 1st and 2nd moieties) which are sensitized to oxidants (see entire document, e.g. page 303, left column lines 28-30 and right column lines 47-51).

Although Gill does not recite a metal-to-phenolic distance for the nickel complex, it is would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to have provided the claimed dimensions, because it is deemed that the metal coordination to tyrosine as taught by Gill would intrinsically provide a Ni-O bond length or Ni:phenolic group distance as instantly claimed. Gill further teaches that providing nickel metal ion, Ni^{+2} , to bovine RNase (adding metal ion to first and second moieties containing metal ligands; polymers/biopolymers/ small molecules) forms multimeric products, including dimers, trimers and higher oligomers thereof (coordination complex, covalent/oxidative crosslinked compound)(e.g. page 303, left column lines 33-38 and right column "Results"). Although Gill does not expressly recite adding metal ligand(s) to a first or second moieties, since Gill teaches that the RNase in the method is obtained from bovine source and said bovine source would necessarily synthesizes the tyrosine-containing (phenolic group or phenolic derivative; tyrosine containing moieties) RNase protein sequence, then obtaining the protein from a bovine source would inherently and broadly and reasonably comprise adding a tyrosine (phenolic group or

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derivative) ligand to each of a first and second moieties (see entire document, e.g. page 303 “Materials”).

Claims 1-24, 26-29 and 31-44 stand as rejected under 35 U.S.C. 103(a) as being unpatentable over Stewart *et al* (U.S. Patent No. 6,087,452) in view of Fancy *et al* (“A Critical Role for Tyrosine Residues in His₆Ni-Mediated Protein Cross-Linking" Biochem. Biophys. Res. Comm. 1998, 247, 420-426.).

Stewart *et al* teaches a method of making a substrate-immobilized composition which said method comprises adding acetic acid (attaching metal ligands) to lysine (first, second moieties) to form a nitrilotriacetic acid (NTA) compound (see entire document, e.g. column 8). Stewart teaches that the compound is contacted with Ni⁺² (metal coordination complex) (e.g. column 9 lines 20-24) and that the complex is further coordinated to polystyrene (PS) beads having added luciferase (metal ligand; phenolic group-, derivative-, nucleophilic/electron donating group-, and tyrosine-containing protein; metalloenzyme)(e.g. column 9 lines 9-24).

Stewart and the instant claims differ in that Stewart does not expressly recite providing horseradish peroxidase (HRP) or crosslinking tyrosine/phenolic groups.

It would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to have provided in the method of Stewart with tyrosinyl residues (phenolic group or derivative) because Stewart teaches (ii) that the metal in the method coordinates with groups, including histidinyl tags and any other tags which are "free to bond with electron-donating or metal-affinity side chains" and that (ii) the reaction may be with a difunctional

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compound (e.g. a poly-His tag) or by co-reaction of the metal chelate with more than one protein wherein each protein contains metal affinity tags (e.g. adding the metal ion-containing chelate to a mixture of tagged proteins) (e.g. column 3 line 46 - column 4 line 7; column 4 lines 43-48).

Furthermore, as taught by Fancy *et al*, providing Tyr-to a His₆ tags (forming a HY-tag), coordinating the HY-tags with a nickel ion (a metal ion, nickel), and cross-linking the Tyr hydroxyl (OH) residues with horse radish peroxidase (HRP) provides a fluorescently detectable cross-linked dityrosine (see entire document, e.g. page 420, abstract, lines 1 through 29; page 421 lines 17-38). Thus one would have been motivated to have provided the method of Stewart with dityrosine groups because one seeking to monitor the coupling reaction of Stewart would recognize from the teachings of Fancy that the oxidative coupling to form dityrosine provides a measurable nickel-enhanced fluorescence in the method. One would have had a reasonable expectation of success because success merely requires tyrosine tagging the compositions in the method of Stewart with the tyrosine of Fancy and reacting the compounds to obtain the covalently cross-linked dityrosinyl group, by reactions known to the person of ordinary skill as taught by Fancy and Stewart and especially in the absence of objective evidence to the contrary.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant has argued that Gill does not teach attaching metal ligands (remarks, pages 17-18) and that the intramolecular moiety is distinguished from the 1st and 2nd moieties.

Regarding Applicant's arguments that the reference does not teach attaching metal ligands; this is not found to be persuasive, because, for the reasons of record, this may be accomplished by the natural process/biosynthesis of the (RNase) amino acid chain.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., inter- vs. intra-molecular complexation/coordination) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, since the compound of the prior art of Gil is broadly and reasonably embraced by the compounds and structural arrangements within the genus of the claims and because the claims do not preclude the combinations of moieties within one or more molecules as disclosed by Gill, then the prior art still renders obvious the instant claims.

Applicant has argued that Stewart and Ho do not teach phenolic groups and teach away from covalent bonding.

Regarding Applicant's arguments that the references do not teach phenolics; this is not found to be persuasive, because, for example Stewart, for the reasons of record teaches that the compounds merely be a his-tag or "any other tags which are 'free to bond with the electron-donating or metal affinity side chains'" (arguments 1/20.2011, at page 11) and because

In response to Applicant's argument that the references teach away from covalent bonding; however, Fancy provides for covalent reaction, including dityrosine reactions, and Stewart (at col 2 lines 28-32) merely teaches metal-to-ligand reversibility and non-denaturing, and does not preclude ligand-ligand covalent reaction therein.

In response to applicant's arguments against the references (Stewart and Fancy) individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claim Objections

Claim 25 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No Claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AARON KOSAR whose telephone number is (571)270-3054. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday,EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/AARON KOSAR/
Examiner, Art Unit 1657

/Christopher R Tate/
Primary Examiner, Art Unit 1655